

The cost-effectiveness of dapagliflozin in heart failure with preserved or mildly reduced ejection fraction: a European health-economic analysis of the DELIVER trial

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Aims

To determine the cost-effectiveness of dapagliflozin, added to usual care, in patients with heart failure (HF) with mildly reduced or preserved ejection fraction for the UK, German and Spanish payers using detailed patient-level data from the Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial.

Methods and results

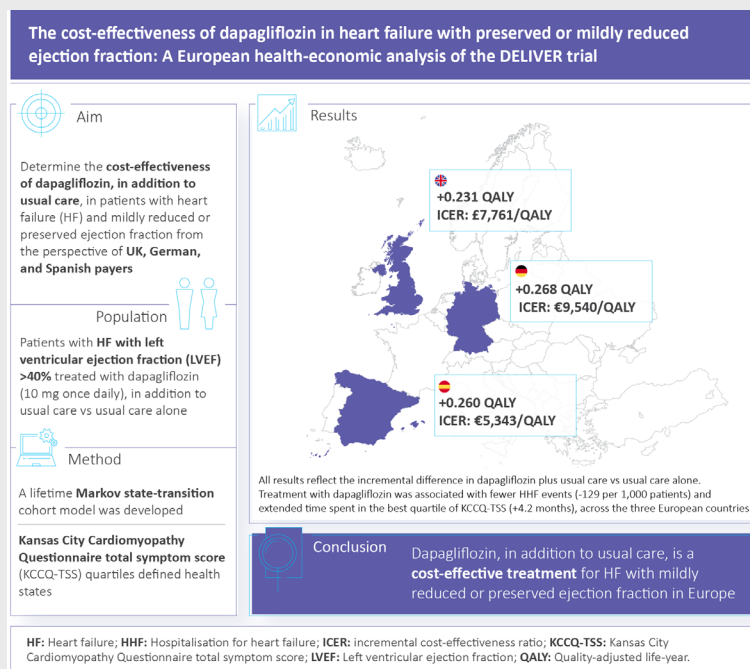
A lifetime Markov state-transition cohort model was developed. Quartiles of the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) defined health states and monthly transition count data informed transition probabilities. Multivariable generalized estimating equations captured the incidence of HF hospitalizations and urgent HF visits, while cardiovascular deaths and all-cause mortality were estimated using adjusted parametric survival models. Health state costs were assigned to KCCQ-TSS quartiles (2021 British pound [GBP]/Euro) and patient-reported outcomes were sourced from DELIVER. Future values of costs and effects were discounted according to country-specific rates. In the UK, dapagliflozin treatment was predicted to increase quality-adjusted life years (QALYs) and life-years by 0.231 and 0.354, respectively, and extend the time spent in the best quartile of KCCQ-TSS by 4.2 months. Comparable outcomes were projected for Germany and Spain. The incremental cost-effectiveness ratios were £7761, €9540 and €5343/QALY in the UK, Germany and Spain, respectively. According to regional willingness-to-pay thresholds, 91%, 89% and 92% of simulations in the UK, Germany and Spain, respectively, were cost-effective following probabilistic sensitivity analyses.

Conclusion

Dapagliflozin, added to usual care, is very likely cost-effective for HF with mildly reduced or preserved ejection fraction in several European countries.

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Graphical Abstract



In this analysis of patient-level data from the DELIVER trial, dapagliflozin added to usual care, versus usual care alone, was very likely cost-effective for the treatment of HF with mildly reduced or preserved ejection fraction for UK, German and Spanish payers.

Keywords

Cost-effectiveness • Dapagliflozin • Heart failure • Mildly reduced ejection fraction • Preserved ejection fraction

Introduction

Heart failure (HF) is a progressive and debilitating condition that can adversely impact a patient's life expectancy and quality of life.^{1,2} HF represents a major global health burden, affecting approximately 64 million people worldwide, with over 15 million cases in Europe.^{3,4} Prevalence is rising alongside the ageing global population and is predicted to increase by 40% from 2015 to 2035.⁵ Responsible for approximately 3 million hospital admissions annually,³ HF represents a leading cause of hospitalization in Europe and is associated with a poor prognosis.⁶ Expenditure for HF accounts for 1–2% of the annual European healthcare budget⁷; hospitalizations for HF (HHF) are a major contributor towards this cost burden.^{8,9} Utilizing effective treatments for HF, which improve patient symptoms and reduce clinical events, has the potential to lessen the high expense of HF management.

Heart failure is subtyped according to left ventricular ejection fraction (LVEF): HF with reduced ejection fraction (HFrEF, LVEF \leq 40%), HF with mildly reduced ejection fraction (LVEF 41–49%), and HF with preserved ejection fraction (LVEF \geq 50%).¹ Existing treatments for HF including renin–angiotensin–aldosterone inhibitors, angiotensin receptor–neprilysin inhibitors,

mineralocorticoid receptor antagonists and beta-blockers, have been shown to improve patient symptoms and reduce risk of HHF and mortality in patients with HF with mildly reduced or preserved ejection fraction is limited, identifying an unmet need in this cohort.¹¹ Sodium–glucose cotransporter 2 (SGLT2) inhibitors, including dapagliflozin and empagliflozin, have emerged as a potential treatment option for patients with HF and LVEF >40% to address the unmet need in this group.^{12,13}

The Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial was a placebo-controlled, phase 3 study in chronic HF patients with LVEF >40% that demonstrated a reduction in the combined incidence of HHF, urgent HF visits (UHFV) or cardiovascular (CV) death (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.73–0.92) with dapagliflozin, added to usual care, versus placebo and usual care (henceforth referenced as usual care alone).¹⁴ Given the current and likely future burden of HF, it is relevant to evaluate the health economic impact of dapagliflozin treatment relative to usual care alone, alongside its clinical efficacy. This is the first study to use full patient-level data from the DELIVER trial to assess the cost-effectiveness of dapagliflozin, added to usual care, versus

usual care alone, for the treatment of patients with HF with mildly reduced or preserved ejection fraction, from the perspective of payers in the UK, Germany and Spain.

Methods

Trial design and outcomes

The DELIVER trial (NCT03619213) was a multicentre, event-driven, randomized, double-blind, placebo-controlled study in patients with HF and a LVEF >40%.¹⁵ The rationale, eligibility criteria and trial design have been described elsewhere.^{15,16} Baseline patient characteristics are outlined in online supplementary Table S1 and published literature.¹⁶ Institutional review boards or ethics committees at individual study sites provided trial approval and all participants provided written informed consent. The primary outcome measured the time to first occurrence of an episode of worsening heart failure (HHF or UHFV for intravenous therapy) or CV death. Secondary endpoints included total number of first and recurrent HF events (HHF or UHFV) and CV deaths (including their individual components), change in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) from baseline to 8 months, and death from any cause.

Economic model

Decision problem and model

To determine the cost-effectiveness of dapagliflozin, added to usual care, versus usual care alone, for patients with HF with mildly reduced or preserved ejection fraction in the UK, Germany and Spain, a Markov state-transition cohort model was developed in Microsoft Excel® (Figure 1). Patient-level data from the DELIVER trial were used to inform the model where relevant. To account for the progressive and chronic nature of HF, the model employed a lifetime horizon with a monthly cycle length, in line with prior HF economic models.^{17–19}

The primary model outcome was the incremental cost-effectiveness ratio (ICER), which was expressed as cost/quality-adjusted life year (QALY) gained. A willingness-to-pay threshold of £20 000/QALY was considered for the UK. As Germany and Spain do not have official willingness-to-pay thresholds, these were derived using the ratio of UK willingness-to-pay threshold versus GDP per capita for 2021. Application of this ratio to national data yielded willingness-to-pay thresholds (rounded) of €25 000 and €15 000/QALY for Germany and Spain, respectively.²⁰ Annual discount rates were applied to future value of costs and effects in accordance with established country-specific rates: 3.5% for the UK and 3.0% for Germany and Spain.²¹ This analysis was conducted according to a pre-specified analysis plan. The model and analysis plan are not publicly available.

Analysis

Base case analysis reflected the overall DELIVER population, with additional analyses of clinically relevant, pre-specified subgroups. Probabilistic sensitivity analysis (1000 seeded simulations) was utilized to quantify the impact of uncertainty around chosen input values; deterministic sensitivity analysis was employed to determine the effect of individual parameters on modelled cost-effectiveness results. This cost-effectiveness analysis conforms to the consolidated health economic evaluation reporting standards (CHEERS 2022) statement.²²

Health states and disease progression

Transitions between discrete health states were used to capture disease progression within the model. Health states were characterized by quartiles of KCCQ-TSS, a patient-reported outcome score which quantifies patients' symptom frequency and severity. Quartiles were chosen to provide sufficient granularity in reflecting disease progression, whilst ensuring ample patient numbers in each health state to result in a statistically robust analysis. The use of health states defined according to KCCQ-TSS quartiles has been reported previously in

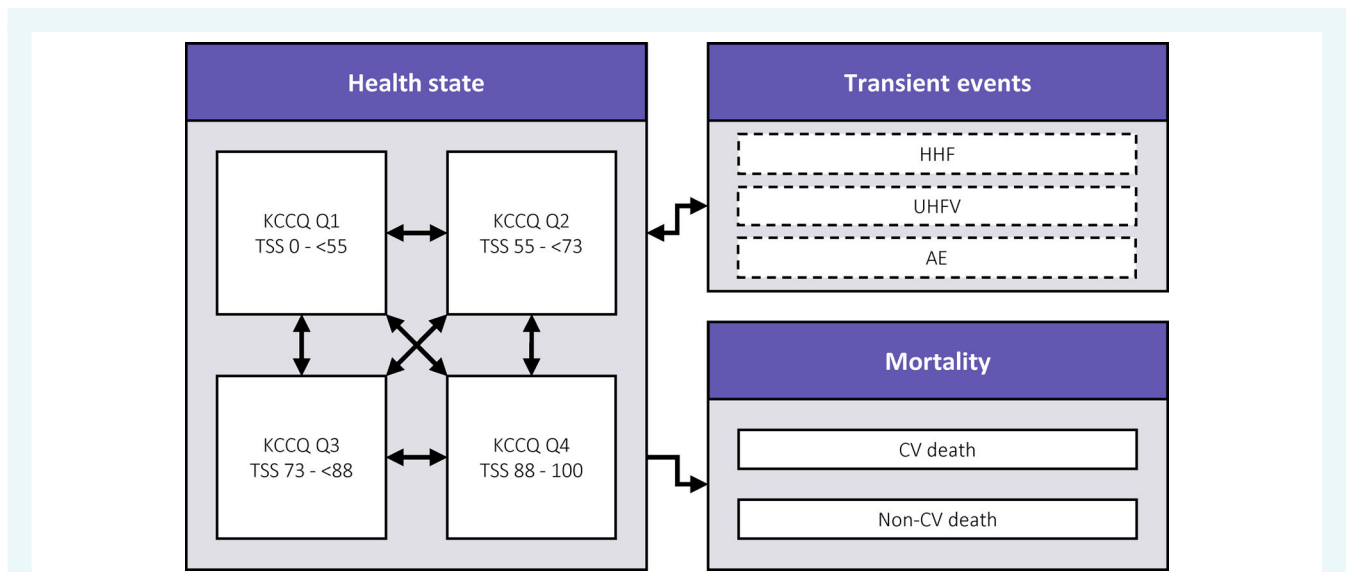


Figure 1 Model structure. AE, adverse event; CV, cardiovascular; HHF, hospitalization for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; Q1–Q4, baseline quartiles of KCCQ-TSS; TSS, total symptom score; UHFV, urgent heart failure visit. Solid boxes relate to health states; dashed boxes relate to non-health state transient events.

cost-effectiveness analysis in HFREF.^{23,24} Monthly transition count data were used to derive transition probabilities between health states, assuming last observation carried forward, whereby patients remained in a KCCQ-TSS quartile until signs of movement. Transition counts used a multinomial likelihood in combination with a flat Dirichlet prior distribution using Gibbs sampling to achieve the posterior probability distribution of the KCCQ-TSS transition matrix.²⁵ Considering a statistically significant change in KCCQ-TSS was observed in the trial,¹⁴ treatment-specific transition probabilities were calculated. Disease progression trajectories were further stratified into a first phase spanning the first 4 months of follow-up data, and a second phase from 4 months onwards. The 4-month split was selected based on previous observation of an inflection in disease trajectory at this timepoint that appears to be characteristic of SGLT2 inhibitors across the cardiorenal spectrum.^{23,26,27} Treatment-dependent monthly transition probabilities are provided in online supplementary Table S2.

Heart failure events, mortality and adverse events

Heart failure events (HHF and UHFV) were estimated using multi-variable generalized estimating equations to model recurrent events. These events were modelled independently of mortality and disease progression. Variables included for adjustment were objectively determined from candidate variables using a forward selection process to optimize regression model fit (online supplementary Table S3). Treatment arm and KCCQ-TSS quartile were included in null models as the minimum components of the analysis to characterize differential risk of HF events according to intervention and health state. All other candidate variables were subject to inclusion or rejection per selection process. Results of the regression are provided in online supplementary Table S4.

Adjusted parametric survival models were used to predict CV deaths and all-cause mortality (ACM). Variables for adjustment were determined using a forward selection approach to optimize model fit. Survival analyses were conducted from an intention-to-treat perspective and were consistent with guidelines for analysis of survival in clinical trials.^{28–30} For the base case analysis, mortality (both CV death and ACM) was assumed to follow a Weibull distribution, following validation of survival extrapolations to previously published long-term observational studies.^{31,32} Coefficients of the survival models are provided in online supplementary Tables S5 and S6. To account for non-CV mortality in the general population, country-specific life tables were adjusted according to data reported by the World Health Organization (WHO) describing sex- and age-stratified country-specific incident rates of CV mortality.³³ This approach removed the risk of any implausibly long predictions of survival and avoided double-counting of mortality.

Adverse events (AEs) included in this model were those classified as serious and with a frequency in excess of 1% of the DELIVER trial population or of special clinical interest, including acute kidney injury, amputation, fracture, urinary tract infection and volume depletion. The risk of experiencing an AE was modelled dependent on treatment arm and applied using a constant hazard (online supplementary Table S7).

Patients in the dapagliflozin arm were subject to constant risk of discontinuation from treatment (6.8% per annum as per DELIVER trial analysis). Upon discontinuation, patients in the model were subject to the same disease progression and risks of HF events, mortality and AE as patients receiving usual care alone. This approach assumes no waning treatment effect and the efficacy of dapagliflozin is instantly lost, consistent with previous modelling of SGLT2 inhibitors.^{23,26,27}

Resource use

Modelled KCCQ-TSS quartile-defined health states were assigned a cost (in 2021 currency British pound [GBP]/Euro). Health state costs were deemed to be reflective of the disease management of patients with HF in each country's healthcare system, with costs covering primary care visits, cardiologist visits and emergency care referrals. The impact of HF events is captured through application of a one-off cost in the cycle of incidence with no subsequent maintenance costs applied. Following the occurrence of an AE, a one-off event-specific cost was applied to reflect the burden associated with AE management. Dapagliflozin costs were applied whilst patients remained on treatment and were considered in addition to the cost of usual care. Upon discontinuation of dapagliflozin treatment, costs of usual care were applied alone. Country-specific cost inputs are reported in online supplementary Table S8.

Health-related quality of life

Health-related quality of life (HRQoL) was characterized by utility weights assigned to KCCQ-TSS quartile health states. For each cycle patients resided in a health state, they accrued the relevant utility to predict total lifetime QALYs. Patients who experienced a transient event (HF event or AE), were assigned a one-off utility decrement applied in the cycle of occurrence.

Modelled utility values were derived from individual patient EQ-5D-5L data recorded during the trial and converted to index scores using country-specific tariffs.^{34–36} Linear mixed effects regression models were fitted to utility index scores to account for repeated per-patient measures and the possibility of random effects. The adjusted models comprised variables determined through a similar forward selection process as was applied for the HF event and survival analyses to reduce the risk of overfitting and limit to relevant parameters (online supplementary Tables S9–S11). Country-specific health state utilities and utility decrements applied in the model are reported in online supplementary Table S12.

Validation

To validate appropriateness of modelling assumptions, results were compared to observed trial data. KCCQ-TSS quartile health state occupancy predicted by the model was overlaid with trial-observed KCCQ-TSS data (online supplementary Figure S1). To account for patient observation time within the trial and associated censoring, event rates for HHF, UHFV and mortalities were compared between observed and modelled results (online supplementary Figure S2). Additionally, survival estimates from the competing risk framework of modelled and general population survival were compared to trial-observed Kaplan–Meier data (online supplementary Figure S3).

Results

For the UK clinical setting, over a lifetime horizon, treatment with dapagliflozin, added to usual care, was predicted to lead to 129 fewer HHF events, 7 fewer UHFV events and 24 fewer deaths from CV causes per 1000 patients (Table 1). Patients receiving dapagliflozin were predicted to have a life expectancy of 8.2 years; an increase of 0.4 years versus patients not receiving dapagliflozin. Patients receiving usual care were predicted to spend 14.3 months in the poorest quartile of KCCQ-TSS (Q1), 13% more than

Table 1 Base case clinical results

Outcome	UK			Germany			Spain		
	Dapagliflozin plus usual care	Usual care	Incremental	Dapagliflozin plus usual care	Usual care	Incremental	Dapagliflozin plus usual care	Usual care	Incremental
Event incidence (per 1000 patients)									
HHF	590.8	719.5	-128.7	589.5	718.4	-128.8	590.8	719.5	-128.7
UHFV	76.8	83.8	-7.0	76.7	83.6	-7.0	76.8	83.8	-7.0
CV death	402.0	425.8	-23.8	400.9	424.8	-23.9	402.0	425.8	-23.8
Time in health state (years, per patient)									
KCCQ-TSS Q1	1.059	1.193	-0.134	1.057	1.191	-0.134	1.059	1.193	-0.134
KCCQ-TSS Q2	1.707	1.678	0.029	1.704	1.675	0.029	1.707	1.678	0.029
KCCQ-TSS Q3	2.155	2.048	0.107	2.151	2.044	0.107	2.155	2.048	0.107
KCCQ-TSS Q4	3.233	2.882	0.351	3.227	2.877	0.350	3.233	2.882	0.351

CV, cardiovascular; HHF, hospitalization for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; TSS, total symptom score; UHFV, urgent heart failure visit.

Table 2 Base case cost-effectiveness results

Outcome	UK			Germany			Spain		
	Dapagliflozin plus usual care	Usual care	Incremental	Dapagliflozin plus usual care	Usual care	Incremental	Dapagliflozin plus usual care	Usual care	Incremental
Total costs	£12 062	£10 267	£1795	€14 496	€11 938	€2558	€12 116	€10 725	€1391
Health states	£6189	£5954	£235	€3965	€3813	€153	€6010	€5778	€233
Clinical events	£3563	£4301	-£739	€6958	€8074	-€1116	€4116	€4832	-€716
Treatment	£2308	£12	£2296	€3573	€52	€3521	€1990	€115	€1874
Total QALYs	4.865	4.633	0.231	5.823	5.554	0.268	5.448	5.188	0.260
KCCQ-TSS Q1	0.492	0.561	-0.069	0.621	0.707	-0.086	0.557	0.634	-0.077
KCCQ-TSS Q2	0.946	0.935	0.011	1.165	1.151	0.014	1.060	1.047	0.013
KCCQ-TSS Q3	1.315	1.257	0.058	1.577	1.506	0.071	1.468	1.402	0.066
KCCQ-TSS Q4	2.143	1.917	0.226	2.491	2.227	0.264	2.393	2.140	0.254
Clinical events	-0.031	-0.036	0.005	-0.032	-0.037	0.005	-0.031	-0.036	0.005
Total life years ^a	8.154	7.800	0.354	8.139	7.787	0.352	8.154	7.800	0.354
ICER (cost/QALY)	-	-	£7761/QALY	-	-	€9540/QALY	-	-	€5343/QALY

ICER, incremental cost-effectiveness ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; QALY, quality-adjusted life year; TSS, total symptom score.

^aLife years are presented undiscounted.

patients receiving dapagliflozin. Conversely, patients treated with dapagliflozin were predicted to spend an additional 4.2 months in the best quartile of KCCQ-TSS (Q4) versus those treated with usual care alone (12% increase). Clinical results were consistent for the German and Spanish settings.

The primary results of the health economic analyses across the three European settings are summarized in *Table 2*. Respectively, in the UK, Germany and Spain, treatment with dapagliflozin added to usual care was associated with incremental costs of £1795, €2558 and €1391 accompanying an increase in QALYs of 0.231, 0.268 and 0.260. The corresponding ICERs were £7761, €9540 and €5343/QALY gained in the UK, Germany and Spain, respectively, below the regional willingness-to-pay thresholds. Incremental costs were driven by differences in treatment, with further increases in health state costs attributable to increased survival in the

dapagliflozin arm. These increases were partially offset by reduced costs associated with clinical events. QALY gains were primarily driven by an increase in time spent in the best quartiles of KCCQ-TSS.

Sensitivity and subgroup analysis

Robustness of the base case results was evaluated by assessing the impact of uncertainty of parameters informing the economic model and of characteristics of subsets of patients. Probabilistic sensitivity analysis for the UK, Germany and Spain yielded simulations of which 91%, 89% and 92% would be considered cost-effective at the respective willingness-to-pay thresholds (*Figure 2*).

When evaluating subgroups of patients, dapagliflozin, added to usual care, remained cost-effective versus usual care alone, with

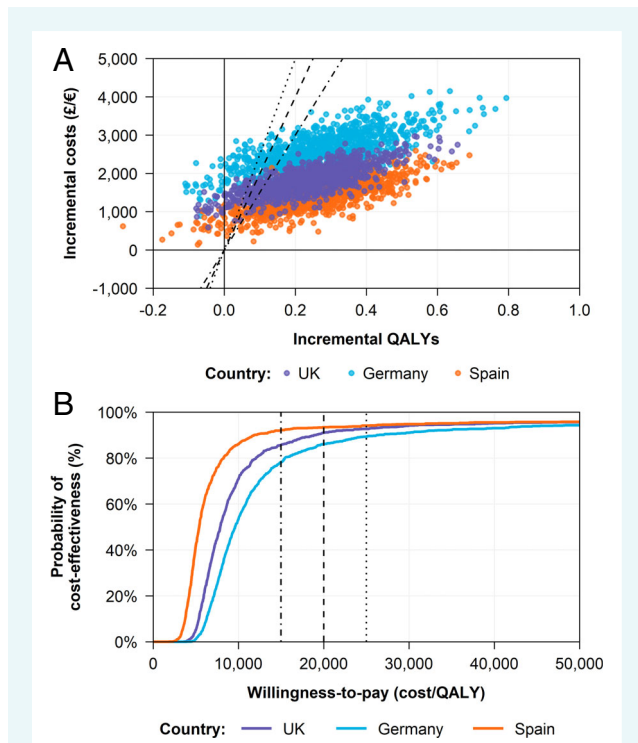


Figure 2 Probabilistic sensitivity analysis. (A) Incremental cost-effectiveness ratio (ICER) scatterplot; (B) cost-effectiveness acceptability curve. QALY, quality-adjusted life year. Black dashed line corresponds to a willingness-to-pay threshold of £20 000 per QALY; black dotted line corresponds to a willingness-to-pay threshold of €25 000/QALY; black dot-dash line corresponds to a willingness-to-pay threshold of €15 000/QALY.

mild deviations in the ICER compared to the base case (Figure 3, online supplementary Table S13). Patient subgroups stratified by those randomized in hospital or within 30 days of a hospitalization (subacute) were found to have the largest impact on cost-effectiveness, with a total deviation versus the base case of £3144, €4527 and €2736/QALY for the UK, Germany and Spain, respectively. In addition, patients with higher baseline N-terminal B-type natriuretic peptide, prior HHF and New York Heart Association (NYHA) class III/IV had the most substantial impact on cost-effectiveness, primarily driven through the greater reduction in HF events and CV deaths. Conversely, subgroup analyses found age, body mass index, and the presence of atrial fibrillation or HF with improved ejection fraction had little effect on cost-effectiveness.

Deterministic sensitivity analysis indicated that cost-effectiveness was robust to changes in input parameters, with all scenarios resulting in ICERs less than regional willingness-to-pay thresholds (online supplementary Figures S4–S6 and Table S14). The greatest drivers of cost-effectiveness were the annual cost of dapagliflozin (ICER ranging from £5774/QALY gained to £9748/QALY gained in the UK setting), discounting on future QALYs and health state utilities (ICERs ranging from €4715/QALY gained to €6650/QALY gained in the Spanish setting). Upon

evaluation of alternative survival extrapolations for CV death and ACM, cost-effectiveness outcomes provided little variation compared to the base case.

Discussion

Informed by the detailed patient-level data of the DELIVER trial, this economic model predicted that dapagliflozin added to usual care, versus usual care alone, is very likely a cost-effective treatment for patients with HF with mildly reduced or preserved ejection fraction for UK, German and Spanish payers. The costs of adding dapagliflozin to usual care were offset by savings associated with an avoidance of clinical events. Additionally, dapagliflozin treatment predicted more patients moved to and/or remained for longer in the best quartiles of KCCQ-TSS, translating into QALY gains (Graphical Abstract).

The management of patients with HF with mildly reduced or preserved ejection fraction is a significant economic burden on healthcare systems, with the long-term costs of HF with preserved ejection fraction thought to be greater than those of HFrEF.³⁷ The cost of hospitalization is a driver of this expenditure,^{38,39} whereby a reduced risk of clinical events may ameliorate this economic burden. The model results indicate that dapagliflozin reduced the incidence of HHF, UHFV and CV deaths versus usual care. This avoidance of clinical events may reduce the resource use associated with HF management, potentially freeing additional capacity for the wider healthcare system. This is an important consideration given the prevalence of HF is predicted to increase,⁵ whereby the use of dapagliflozin may reduce future challenges with demand of healthcare services. Given the results were consistent across the three healthcare settings modelled, where any key differences were attributed to the varying acquisition costs of dapagliflozin and EQ-5D utility inputs for each setting, these findings may be generalizable to other EU markets.

Recent studies have assessed the cost-effectiveness of the SGLT2 inhibitor, empagliflozin, in various non-European countries in a similar patient population.^{40–42} Unlike these prior studies that used aggregate data from trial publications, this present analysis was performed on individual patient-level data from the DELIVER trial. While both approaches are valid, the present analysis allows for the adjustment of patient characteristics to reproduce the trial-observed effects on mortality, events and HRQoL. Utilizing patient-level data, as opposed to average aggregated trial outcomes, allows the model to predict changes in patient KCCQ-TSS score over time and does not rely on a pre-specified endpoint in the trial data, thus may capture disease progression more accurately. Further, as the modelled utility values were derived from individual patient EQ-5D-5L data from DELIVER, this allows for the adaptation of country-specific index scores using their respective tariffs. The use of patient-level EQ-5D-5L data removed the need for mapping algorithms to obtain utilities associated with health states, and their associated limitations.⁴³ Additionally, using patient-level data enabled broader health states to be modelled, thereby providing a greater understanding of disease severity and its impact on patient quality of life. Lastly, because the model fully utilized the

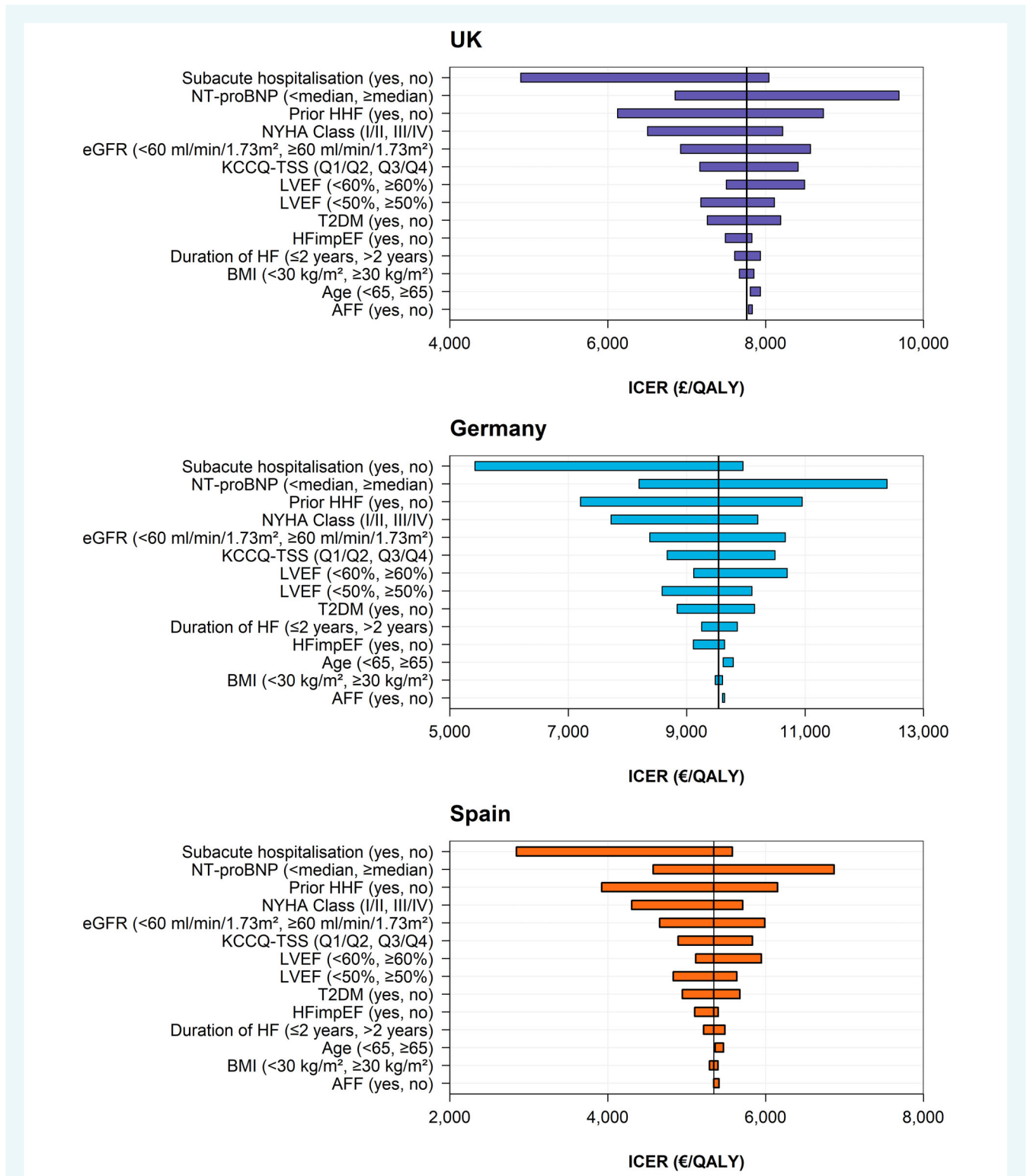


Figure 3 Subgroup analysis. AFF, atrial fibrillation/flutter; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; HHF, hospitalization for heart failure; ICER, incremental cost-effectiveness ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QALY, quality-adjusted life year; T2DM, type 2 diabetes mellitus; TSS, total symptom score.

trial data and therefore was less reliant on simplifying assumptions, the inter-correlation of the variables within each patient could be accounted for, resulting in a more precise and less biased health economic evaluation.

The NYHA class is commonly used to characterize disease state in patients with HF. However, NYHA functional classification has several limitations including, subjectivity, heterogeneity and a lack of patient-centric HF assessment.^{24,44} Given NYHA class I patients were excluded from the DELIVER trial and 75% of the overall DELIVER trial population was NYHA class II at baseline,¹⁴ precise modelling of disease progression based on NYHA classification would have been difficult. To more accurately model the long-term HF progression, discrete health states characterized by patient-reported KCCQ-TSS quartiles, as opposed to clinician-reported NYHA functional class, were used in the analysis. The four health states (KCCQ-TSS quartiles) and EQ-5D data could be directly attributed to the time spent in each state. Utilizing KCCQ-TSS quartiles over NYHA class meant that a broader spectrum of HF severity and the associated patient quality of life over time could be more sensitively modelled. As KCCQ approaches have been reported to be more sensitive to clinically meaningful changes in health status over time than NYHA class,⁴⁵ there may be value in generating a consistent modelling approach for a broad HF disease model based off these methods.

A typical patient population with HF with mildly reduced or preserved ejection fraction is likely to be older and more comorbid than a population with HFrEF.^{46,47} Therefore, it could be expected that survival may be a less critical outcome measure for this patient population than changes or improvements in quality of life. The analytical approach of the present study relied upon risk equations derived from trial data and results as observed in the DELIVER trial. A notable consequence of this approach is that the mean effects of the trial as observed are reproduced in the modelling, including components of composite endpoints such as CV death or HHF separate from UHFV events, regardless of whether they individually reach the pre-defined threshold of statistical significance. The model results indicate that extrapolation of DELIVER trial data shows some longer-term mortality benefit for dapagliflozin treatment. However, due to the lack of data on the long-term effects of dapagliflozin in patients with HF with mildly reduced or preserved ejection fraction, it is unknown whether these findings would be replicated in real-world practice, thus further research is warranted.

Several potential limitations of this analysis exist. First, the model required extrapolation beyond the observed trial period of DELIVER. Observed similarity of extrapolated model survival results with observational community studies of patients with mildly reduced or preserved ejection fraction supported the relevancy of the modelling approach. Also, trial observations of HRQoL may be higher than those of general practice for both the placebo and dapagliflozin arm due solely to the frequency of healthcare contact. Second, as the study is focused on HF outcomes, additional healthcare costs such as non-HF management or hospitalization costs could not be quantified as these were not part of the adjudicated trial data. Third, owing to the Markov state-transition structure of the model, individual patient histories could not be

tracked, meaning that subsequent health-related consequences of events were not captured. For example, after an event of HHF, long-term costs relating to discharge to a managed care facility and any rehospitalization or mortality would not be readily tracked. Additionally, the independent, separate modelling of these recurrent HF events meant that subsequent effects on worsening HF or increased mortality risk were not captured. As the clinical trial demonstrated a benefit on recurrent HF events, this simplifying estimation in support of model parsimony makes the presented results a conservative estimate of potential benefit of reducing the incidence of primary events. Last, due to a lack of studies describing the healthcare burden of HF with mildly reduced or preserved ejection fraction, resource use inputs were sourced from studies based on the HFrEF patient population.

Overall, the model results indicate that dapagliflozin, added to usual care, is very likely to be a cost-effective intervention for patients with HF with mildly reduced or preserved ejection fraction in the UK, Germany and Spain, according to respective willingness-to-pay thresholds. The model predicts that dapagliflozin, added to usual care, may reduce the incidence of HF events and increase the time spent in the best quartiles of KCCQ-TSS, translating into QALY gains and important offsets to the cost of treatment.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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